## REMARKS

Reconsideration of the present application is respectfully requested.

**Status of the Claims**

Claims 152 to 170 have been acted upon by the Examiner. No claims have been amended, canceled or added. Accordingly, Claims 152 to 170 are presented for examination.

**Obviousness Rejections**

All previously pending obviousness rejections that relied on the combination of Goodey *et al.* (WO 97/31947) and Johnson *et al.* (U.S. Patent No. 5,625,041) have been withdrawn.

Claims 152 to 170 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goodey (WO 97/31947), Dromard (U.S. Patent No. 4,675,384), Fisher (U.S. Patent No. 4,228,154), Ohmura (EP 0 570 916 A2), and Tayot (Develop. Biol. Standard., vol. 67, pp. 15-24, 1987).

Applicants first note that the combination of Goodey with Fisher or Ohmura et al. has been asserted previously in prior Office Actions and the combination has been found not to render previously-pending related claims obvious. See, for example, Reply dated August 10, 2005.

In presenting the *prima facie* case of obviousness, the Examiner primarily relies on Goodey. See Action at 3-6. The Examiner, however, concedes that Goodey does not teach albumin purification using cation exchange (CE) or anion exchange (AE) chromatography run in the negative mode which are recited in presently pending

claims. Action at 6. For these recitations, the Examiner relies on Dromard, Fisher, Ohmura or Tayot. The Examiner also seems to imply that Tayot teaches a loading concentration of 31 g/L for a negative CE chromatography step. Action at 7. The Examiner further asserts that the motivation to combine these teachings is provided by Fisher which teaches that negative chromatography "minimized potential alterations in the native structure of albumin and such reduction in handling or manipulation was advantageous in commercial applications" and Tayot which states that "[t]he low volume of the 3rd column (cation exchanger) is due to the deliberate choice of fixing the impurities selectively without fixing the albumin. It is more economical to fix the minority components than the main protein." Action at 7.

"To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143. Here, there is no suggestion or motivation to combine the references, and the references when combined do not teach or suggest all the claim limitations.

## I. Goodey and Dromard

### A. There is no motivation to combine Goodey *et al.* and Dromard *et al.*

"Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so." M.P.E.P. § 2143.01. While the Supreme Court's recent decision in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007) cautioned against applying the teaching, suggestion, motivation test in a rigid manner, the Court

acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements [or, in the case of single reference, to modify the reference] in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Here, there is no such reason.

Independent claims 152 and 167 of the present application are directed to the isolation of recombinant albumin and specifically include the recitation "wherein the albumin solution is a recombinant albumin solution." Insofar as it is relevant to the present application, Goodey is also concerned with the purification of recombinant albumin. By contrast, Dromard is concerned with purification of albumin from plasma. This is abundantly clear from, *inter alia*, the abstract; col. 1, line 65; and col. 2, lines 1-10; in conjunction with col. 1, lines 13-15 which makes the point that the major difficulty of obtaining albumin from plasma is its separation from the other major component, immunoglobulins, and Examples 1-4 which clearly show a continued contamination of albumin products with α-Globulins and β-Globulins. Dromard's methods are clearly designed and optimized to separate albumin from various immunoglobulin molecules.

Isolation of recombinant albumin represents a different technical challenge to the isolation of plasma-derived albumin. Host cell derived contaminants present in unprocessed recombinant albumin preparations are different in their physical and chemical properties to plasma derived contaminants like immunoglobulins. For example, a recombinant albumin purification process using a yeast system would have contaminants such as mannosylated proteins, yeast derived pigments, and cell wall components. Accordingly, a person of ordinary skill looking to optimize the process of Goodey would not consult Dromard which is directed to overcoming the problems

of purifying albumin from plasma and the associated plasma-derived contaminants (e.g., immunoglobulin, haptoglobin, transferrin and $\alpha_1$-acidic glycoprotein).

Accordingly, the person skilled in the art would not be motivated to combine Goodey and Dromard in order to arrive at a method of isolating recombinant albumin, as claimed in Claims 152 and 167.

**B. The combination of Goodey and Dromard fail to disclose or suggest an albumin concentration for negative mode CE of 10-250 g/L or that using such a concentration would have been successful**

The only pending independent claims 152 and 167 recite that "the albumin solution subjected to the cation exchange chromatography step that is run in the negative mode with respect to albumin has an albumin concentration of 10-250$g.L^{-1}$." Applicants submit that neither Goodey nor Dromard discloses at least the aforementioned feature of independent claims 152 and 167.

Goodey does not disclose this feature. In respect of this feature, the examiner has pointed to passages in Goodey at page 21, line 8; page 23, line 25; page 24, line 23; page 32, lines 10 and 25; page 33, line 21; page 37 line 10; and page 39, line 9. In our previous Reply dated June, 12 2007, we provided the examiner with a detailed explanation of the disclosure of each of these passages – none of them disclose that albumin should be loaded onto a negative mode CE step at a concentration of 10-250 g/L. If this rejection is maintained – *and it should not* – applicants respectfully request that the Examiner address applicants' comments with regards to these passages.

Likewise, Dromard also fails to disclose a loading concentration of 10-250 g/L for a negative mode CE step. There is no indication in Dromard that the loading

concentration for a negative mode CE step is considered to have any importance whatsoever. For example, Examples 1-4 of Dromard report the loading concentration of the CE step as a mere incidental feature, and the document places no technical importance on the concentration used therein. The lack of technical importance for the loading concentration of the negative mode CE step is highlighted by the fact that none of Examples 5-13 even bother to mention the loading concentration used for the negative mode CE step. The clear teaching to the reader of Dromard is that loading concentration for the negative mode CE step is unimportant.

Moreover, where loading concentrations for this step are disclosed, they are all lower than 10-250 g/L.

- Example 1 (col. 11, lines 36-53) of Dromard discloses that a protein solution having 4.2 g/L and containing 96.5% albumin (i.e. 4.053 g/L of albumin) is further diluted by pH adjustment and addition of sodium chloride, and then loaded onto a CE column ("Column III") in the negative mode to produce an albumin having a purity of 99.5% (i.e. 0.5% impurity).

- Example 2 (col. 12, lines 29-47) teaches that the albumin purity was worse (just 99.0%, i.e. 1.0% impurity) than that obtained in Example 1, when a protein solution having 10.1 g/L protein, of which 95.0% was albumin (i.e. 9.595 g/L of albumin), is loaded onto a CE column in the negative mode.

- Example 3 (col. 13, lines 1-17) reports that the albumin purity was, again, worse (just 99.1% albumin, i.e. 0.9% impurity) than that obtained in Example 1 when a protein solution having 7.5 g/L protein, of which 95.3% was albumin (i.e. 7.1475 g/L of albumin), is loaded onto a CE column in the negative mode.

- Example 4 (col. 13, line 65 to col. 14 line 12) teaches that the highest level of purity (100%, i.e. 0.0% impurity) was obtained when a protein solution having 3.06 g/L of protein, of which 93.6% was albumin (i.e. 2.86 g/L of albumin), is loaded onto a CE column in the negative mode.

Thus, if one of skill in the art did consult Dromard for guidance on the loading concentration to use (for which there is no reason), then it is clear that one of skill in the art would be motivated to use a loading concentration of less than 10 g/L (i.e. below the lower limit of Claims 152 and 167), since all of Examples 1-4 use concentrations that fall below this limit. Accordingly, one of skill in the art would not be motivated from Dromard to use any particular loading concentration, and that both Goodey and Dromard, individually or in combination, fail to teach or suggest the step of loading a negative mode CE step with an albumin solution that an albumin concentration of 10-250 g/L.

In fact, Dromard teaches away from using a loading concentration of greater than 10 g/L. "A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness . . . ." M.P.E.P. § 2145. To the extent that one of skill in the art would take any guidance from Dromard at all in respect of the albumin loading concentration to use for a negative mode CE step then, from a detailed reading of Examples 1-4, it would be clear to the reader that lower loading concentrations should be favored. This is evident from the following summary of the results in Examples 1-4 of Dromard, which shows the results in order of the level of purity achieved, and the level of improvement in (i.e. removal of) impurities. (Starting and final levels of impurity are calculated by subtracting the percentage level of albumin purity stated in Dromard from 100%; the value of improvement in purity is calculated by dividing the starting level of impurity by the final level of impurity.)

| Example | Albumin loading concentration | Starting level of impurity | Final level of impurity | Improvement in albumin purity |
|---|---|---|---|---|
| 4 | 2.86 g/L | 6.4% | 0.0% | Infinity |
| 1 | 4.053 g/L | 3.5% | 0.5% | 7.0-fold |
| 3 | 7.1475 g/L | 4.7% | 0.9% | 5.2-fold |
| 2 | 9.595 g/L | 5.0% | 1.0% | 5.0-fold |

From the foregoing summary, it is clear that the highest level of purity, and the largest fold-improvement in albumin purity, was achieved with the lowest loading concentration (2.86 g/L) used with a negative mode CE step. By contrast, the highest loading concentration resulted in the lowest level of purity and the smallest fold-improvement in albumin purity.

Thus, the data in Examples 1-4 of Dromard can clearly be taken by the skilled person as in indication that, at the very least, an albumin loading concentration of about 2.86 g/L is favored and, moreover, that increasing the loading concentration of the albumin in the material loaded onto a negative mode CE step would be detrimental to product purity. Based on these teachings by Dromard, one of skill in the art would not have reasonably expected success by using a concentration of 10-250 g/L of albumin in a negative CE step.

As discussed in prior replies, applicants have found that using such a loading concentration when purifying recombinant albumin (rather than plasma-derived albumin as used in Dromard) resulted in unexpected and surprising results. Such higher loading concentrations for recombinant albumin solutions with negative mode cation exchange chromatography provides for more efficient recovery of albumin, and, at the same time, result in impurities from the recombinant system being more

efficiently removed. See Reply to Office Action dated November 14, 2005 dated May 15, 2006 and the Declaration Stephen Berezenko filed therewith.

Accordingly, any obviousness rejections based on the combination of Goodey and Dromard should be withdrawn.

**II. Goodey and Fisher**

The Examiner asserts that Fisher teaches purification of albumin using CE and AE steps run in a negative mode with respect to albumin. Action at 7. Moreover, the Examiner asserts that the motivation to combine the negative mode steps of Fisher with Goodey is that Fisher teaches that negative mode steps "minimized potential alterations in the native structure of the albumin and reduction in handling or manipulation was advantageous in commercial applications." Action at 7.

Applicants note that an obviousness rejection over the combination of Goodey and Fisher has already been asserted by the Examiner and withdrawn based upon claim recitations in the presently pending claims. See applicants' remarks in Reply to Office Action dated March 10, 2005 dated August 10, 2005 and subsequent Office Action dated November 14, 2005 in which the Examiner states that "applicants' amendments overcame the rejections presented previously." In summary, the combination of Goodey and Fisher was withdrawn in view of the following arguments submitted in applicants' Reply dated August 10, 2005.

- The teachings of Goodey and Fisher are incompatible, because Fisher teaches that one should avoid method steps that require desorption of albumin, whereas Goodey's method which involves positive mode CE and AE steps requires binding and then desorption of the albumin. Accordingly, the reader of Fisher would not consult Goodey or consider using its method steps.

- Neither Goodey nor Fisher discloses a loading concentration of 10-250 g/L albumin for the negative mode CE step. Neither does either of these documents

> suggest that loading concentration is an important parameter for optimising the purification and recovery of albumin from a negative mode CE step. As discussed above, applicants found that such loading concentrations resulted in surprising and unexpected results.

For a more complete discussion of the above, please see applicants' Reply to the Office Action dated March 10, 2005, dated August 10, 2005.

Accordingly, the obviousness rejection based on the combination of Goodey and Fisher should be withdrawn.

**III. Goodey and Tayot**

Like Dromard discussed above, Tayot relates to the purification of albumin from plasma. Tayot discloses a 3 step ion exchange method, involving DEAE SPEROSIL W-1000, then QMA SPHEROSIL PH-1000, then COOH-SPEROSIL W-1000 (abstract and Table II on page 20). Page 19 teaches that the third step (i.e. the COOH-SPEROSIL W-1000) is a CE step, whereas the QMA SPHEROSIL PH-1000 is a AE step. The first step (DEAE SPEROSIL W-1000) is also an AE step (see Ohmura, page 6, lines 11-15). Thus, Tayot describes a method of purifying serum albumin using AE, then another AE step, then CE. Page 19, (ii) makes it clear the first AE step is in the positive mode with respect to albumin and the captured albumin must be eluted in an elution buffer. Page 19, (iii) makes it clear that the third (CE) step is in the negative mode with respect to albumin. It appears from Table II on page 20 that the second (AE) step may also be in the negative mode. Further, Table II on page 20 shows that the plasma is subject to filtration, clarification, 2 centrifugations and a further filtration step before any of the ion exchanges steps are performed.

First, one of skill in the art would not be motivated to combine the teachings of Goodey and Tayot. As discussed above with respect to Dromard, the isolation of

recombinant albumin from a host cell culture represents a different technical challenge from the isolation of albumin from serum, since they have different contaminants and require different conditions in order to isolate the albumin protein. Accordingly, a person of ordinary skill looking to optimize the process of Goodey would not consult Tayot.

Second, the combination of Goodey and Tayot fail to disclose or suggest an albumin concentration for negative mode CE of 10-250 g/L. The Examiner has noted that page 20 reports that plasma containing 31 g/L is used at the onset of the method. However, this initial plasma preparation passes through multiple steps (as shown in Table II on page 20 - filtration, clarification, 2 centrifugations, 0.2 μ filtration, the first (positive mode) AE step, and the second (seemingly negative mode) AE step) prior to the negative mode CE step, and there is no disclosure of what concentration of albumin was applied to this negative mode step. Tayot fails to disclose any particular albumin concentration should be used for the negative mode CE step, and entirely fails to appreciate that loading concentration is an important parameter for optimising yield and purity. Therefore, for the same reasoning as explained in the Reply dated January 8, 2007 in regard to the Examiner's allegation of obviousness based on the combination of Goodey and Matsuoka, even if the person skilled in the art did seek to apply the method steps of Tayot to Goodey's method, the concentration of albumin used would be a consequence of the production method taught in Goodey, and then further diluted by the initial steps in Tayot's method before being applied to Tayot's negative mode CE step. There is nothing in Goodey that would result in the skilled person selecting an albumin concentration to apply to Tayot's CE step within the range 10-250 g/L.

Consequently, even if the person skilled in the art did seek to apply the method steps of Tayot to Goodey's method, for which there is no motivation in view of their

different technical considerations (i.e. one being related to purification of recombinant albumin, the other to serum albumin) then nevertheless, there is no motivation to apply Tayot's method in such a way as to ensure that the negative mode CE step is loaded with recombinant albumin that has a concentration of 10-250 g/L.

Accordingly, any obviousness rejections based on the combination of Goodey and Tayot should be withdrawn.

**IV. Goodey and Ohmura**

The Examiner relies on Ohmura for the purification of recombinant human serum albumin using CE chromatography in the positive mode and AE chromatography in the negative mode. In particular, the Examiner points to a passage in Ohmura (page 3, lines 1-9) that discloses a multi-step method for purifying recombinant albumin that includes, as the fifth step, a positive mode CE step, then as the sixth step a hydrophobic chromatography step, then as the seventh step a negative mode AE step. The other passages identified by the Examiner add nothing further to this.

There is no disclosure in Ohmura of a CE step that is run in the negative mode with respect to albumin. Nor does it disclose that a negative mode CE step should be loaded with 10-250 g/L albumin. Indeed, Ohmura places no importance on the loading concentration of albumin for any ion exchange step, much less a negative mode CE step. Thus, Ohmura does not cure the deficiencies of the combined teaching of Goodey, Fisher, and Tayot discussed above.

Accordingly, even if one of skill in the art did combine the teachings of Goodey and Ohmura, along with the other art discussed above, then they would not

arrive at method that involves the step of negative mode CE with respect to albumin at all, much less one that is loaded with a 10-250 g/L albumin solution, since neither of these documents disclose these features. Thus, the combination of Goodey and Ohmura do not overcome the deficiencies of the other references discussed above.

**Conclusion**

In view of the foregoing amendments and remarks, applicants assert that the claims are in condition for allowance, and request respectfully issuance of a Notice of Allowance. If there are any issues remaining, applicants request an interview prior to the issuance of an action. If any additional fees are required to continue the prosecution of this application, please charge such fees to Deposit Account 19-5425.

Respectfully submitted,

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